

THIS MONTH IN THE JOURNAL

Analysis of BRCA1/2 Unclassified Variants, by Easton et al. (p. 873)

Screening of *BRCA1* and *BRCA2* has enabled a large number of patients and their families to assess their risk of developing breast cancer. In many cases, the results are clear-cut; a known truncating mutation is found, and the effect on breast cancer risk is understood. Unfortunately, there is a growing list of identified variants for which the association with disease risk is unknown. The ambiguities of the effects of these sequence changes pose a significant problem for genetics counseling, so various strategies have been developed to determine the clinical significance of the variants. Easton et al. compiled family data, cosegregation information, and frequency statistics from thousands of individuals, to establish the potential role of 1,433 sequence variants in causing disease. Additionally, the authors were able to create a list of sequence changes for which the odds of being deleterious were high and another list of those variants for which the odds of being a risk allele were low. The hope is that the results reported here will contribute to the arsenal of information for use in genetics counseling and that patients will benefit from more-reliable risk assessment.

Mutation of FAM20C in Raine Syndrome, by Simpson et al. (p. 906)

Raine syndrome is an autosomal recessive condition of aggressive and lethal osteosclerotic bone dysplasia. Neonates affected with the disease usually die after only a few days or weeks. Analysis of a patient with Raine syndrome revealed a chromosomal rearrangement that resulted in the fusing of both copies of chromosome 7 and a loss of material from the 7p telomeres. Five genes reside in the affected region, and Simpson et al. suspected that the loss of one of these genes, *FAM20C*, was linked to Raine syndrome, because of their previous findings that the mouse *FAM20C* ortholog was involved in odontoblast differentiation and mineralization. Mutation screening of *FAM20C* in six other patients with Raine syndrome identified four missense mutations involving conserved residues and four splice-site mutations that were predicted to severely reduce or abolish splicing. Subsequent mouse *in situ* hybridization studies localized the gene to mineralizing surfaces of the somites and limb girdle, as well as to the osseous, odontoblasts, and ameloblasts.

Northern Asian mtDNA, by Derenko et al. (p. 1025)

High-resolution analysis of mtDNA, including the complete sequencing of mtDNA genomes, has contributed a great deal to the understanding of the timing and direction of human dispersions around the world. There is previous evidence that ancestral populations from northern Asia migrated to the Americas, but questions remain about the details of their migrations to northern Asia. Previous work supports a southern migration route out of Africa to India, East Asia, and Australasia. Also, on the basis of archaeological findings, it has also been hypothesized that a second exodus from Africa took a more northern route to northern Asia through central Asia and southern Siberia. No genetic evidence has been found to support a second migration out of Africa to northern Asia, but previous studies have been hampered by small sample sizes. Derenko et al. sought to clarify this issue by analyzing the mtDNA of individuals from 18 populations living throughout the region. The authors do not find any data that support a northern Asian migration route out of Africa, but they do predict that there were at least two migrations into southern Siberia, one from western Eurasia and one from East Asia.

Protein Therapy of Ectodermal Dysplasia, by Casal et al. (p. 1050)

X-linked hypohidrotic ectodermal dysplasia (XLHED)—characterized by tooth abnormalities, decreased hair development, and a lack of glands, which leads to decreased sweat production and increased infections—is caused by mutations in ectodysplasin A (EDA). There is evidence that treatment of the mouse model of XLHED with recombinant EDA (Fc:EDA1) can rescue many of the disease phenotypes, but it was determined that only prenatal, not postnatal, administration is able to correct the abnormal tooth development. Postnatal treatment would be more useful in humans, because the XLHED diagnosis usually is not made before birth. Casal et al. predicted that the dog model, rather than the mouse model, of XLHED would more closely resemble the human disease, because the timing of the tooth development in dogs is more similar to that in humans. Therefore, the authors suspected that postnatal administration of Fc:EDA1 in dogs would be able to rescue the dental phenotype and would also predict how such treatment would affect humans more accurately than would treatment in mice. Casal et al. treated several XLHED-affected dogs with various treatment regimens of Fc:EDA1 injections. Treated dogs showed a significant im-

provement in sweat and tear production, as well as improved dental development. The hope is that these data will contribute to the ongoing work for the successful treatment of XLHED in humans.

Microdeletion of 17q12 Causes Diabetes, by Mefford et al. (p.1057)

The recurrent microdeletions or microduplications that characterize genomic diseases are thought to often be generated by chromosomal rearrangement facilitated by segmental duplications. A BAC array was previously created that targeted regions containing segmental duplications, because it was suspected that these sites would be frequently involved in genomic rearrangements. Use of the array in a number of unaffected and patient populations has revealed that many of the predicted hotspot regions were not regularly part of microdeletions or microduplications. Mefford et al. hypothesized that disruptions of some of the sites may be incompatible with life, so they chose to use the BAC array on fetal samples for which the phenotypes were well established. Within this patient population, the authors identified a microdeletion at 17q12 in a sample with grossly abnormal, dysplastic, multicystic kidneys. The microdeletion spanned 1.8 Mb and encompassed 19 known genes, including *TCF2*, a gene known to be mutated in maturity-onset diabetes of the young type 5 (MODY5) and cystic renal disease. Analysis of previously identified patients with MODY5 and cystic renal

disease revealed that many of them carried the same rearrangement, resulting in the identification of a genomic disorder due to the recurrent microdeletion at 17q12.

This Month on the Cover

Because human mtDNA is inherited maternally, does not undergo recombination, contains regions with a high mutation, and is found in high copy numbers in human cells, mtDNA has become a powerful tool for studying human evolution. Analysis of mtDNA lineages, or haplogroups, can be used to establish shared maternal ancestry among populations. This allows investigators to assess the prehistory of individual populations, establish migration and colonization timelines, and investigate population admixture. Additionally, because of the stability and abundance of the molecules, mtDNA has also been useful in the realms of forensic science and the study of ancient DNA. On the cover is the genealogical tree from one of the first reports of the use of mtDNA to examine the maternal ancestry of populations from around the world (Nature 325:31–36). Analysis of 147 samples from five geographic regions supported the hypothesis that the studied people all shared a common, likely African, maternal ancestor. (Figure reprinted by permission from Macmillan Publishers: Nature [325:31–36], copyright 1987.)

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